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MEMORANDUM

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Subject: Benchmark dose calculations on TSH and thyroid hormones from Effects Protocol, Argus 1416-003 (Argus, 2001)

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This memo is to transmit results of EPA benchmark dose analysis on TSH and thyroid hormone data in the study entitled *Hormone, Thyroid, and Neurohistological Effects of Oral (Drinking Water) Exposure to Ammonium Perchlorate in Pregnant and Lactating Rats and in Fetuses and Nursing Pups Exposed to Ammonium Perchlorate during Gestation or via Maternal Milk* (Argus, 2001). The samples used in this analysis were derived from rats treated with ammonium perchlorate (AP) in drinking water during pre-pregnancy, gestation, and lactation at doses of 0.00, 0.01, 0.1, 1.0, and 30 mg/kg/day. Data were considered from males and females separately, then combined, as well as the dams, from the following timepoints: gestational day 21 (GD21), post-natal day (PND) 4, and PND 21. Because of disparities between USEPA and Argus/Primedica nomenclature, these latter three timepoints correspond to PND 5, PND 10, and PND 22 in Argus, 2001.

Benchmark dose / lower confidence limits on benchmark dose (BMD/BMDL) were generated using the BenchMark Dose Software v. 1.30, publically available from the USEPA. A benchmark response of 1 control standard deviation from the control mean was adopted in conjunction with fitting the data with a Hill equation constrained such that $n \geq 1$:

$$Y(\text{dose}) = \text{intercept} + v * \text{dose}^n / (k^n + \text{dose}^n)$$

The Hill equation was chosen as a flexible form given the nature of the observed responses; i.e. non-linear monotonic functions saturating at higher doses. The 1 SD BMR was chosen to take advantage of the following relationship. If values beyond the 98th to 99th percentile of control animals are considered abnormal, a dose that causes a shift in the average of 1 sd yields an

approximate excess risk of 10% of the animals in the abnormal range (W. Setzer, pers. comm, Crump, 1995). While the USEPA has expressed reservations about using this type of criterion because it rewards a broad distribution in the control data by pushing the benchmark response to higher doses, in this case it seemed reasonable given that the data for almost all cases showed a consistent coefficient of variation of approximately 10%, i.e., control values were not inflated beyond other dose groups nor was the variability beyond what is commonly seen in experimental studies. A chi-squared test was used to determine the goodness-of-fit of these functions.

Table 1 shows the BMD/BMDL for TSH, T4, and T3 for the dams and pups assayed in the "Effects" study (Argus, 2001). In many cases, the BMDL was not calculable because the criterion for the BMDL lay outside of the range of values fitted to the dose response. This is likely due to the observed asymptotic effects of ammonium perchlorate on iodide uptake. The range of BMDLs for TSH is 0.004 - 0.53 mg/kg, for T4, $2.9\text{e-}7$ - 0.004 mg/kg, and for T3, 0.001 - 0.13 mg/kg. These values reflect an extreme sensitivity to ammonium perchlorate exposure such that there were measurable changes in TSH and thyroid hormones at the lowest dose tested.

References

Argus Research Laboratories, Inc., 2001. *Hormone, Thyroid, and Neurohistological Effects of Oral (Drinking Water) Exposure to Ammonium Perchlorate in Pregnant and Lactating Rats and in Fetuses and Nursing Pups Exposed to Ammonium Perchlorate during Gestation or via Maternal Milk*. Argus Research Laboratories, Inc., 2001.

Table 1: Benchmark dose and benchmark dose lower confidence limits from thyroid hormone data (Argus, 2001) after dosing with ammonium perchlorate (AP). Data is fit with Hill function, with exponent n restricted to be > 1 , with a BMR of $1.0 \times$ standard deviation (SD) of controls.

Study Population "Effects" Study (Argus, 2001)	BMD BMDL mg/kg		
	TSH	T4	T3
GD 21 Dams	1.63 NC	0.006 0.004	2.38 NC
GD 21 Fetal pups	0.82 0.49	0.084 NC	0.003 0.001
PND 4 M + F (culled) pups	0.65 0.12	0.004 $3.56e-7$	NC NC
PND 21 Dams	1.07 0.53	3.98 NC	NC NC
PND 21 Male pups	0.009 0.004	0.001 $2.86e-7$	3.71 0.13
PND 21 Female pups	0.59 0.23	NC NC	NC NC
PND 21 M + F pups	0.06 0.02	NC NC	NC NC

NC: not computable. In many cases this was because the benchmark response defined as 1 standard deviation from control was outside of the range of the dose response, even though in most cases there was a clear dose response to AP